Lab Design

Setting Up a Lab For Optimal Performance
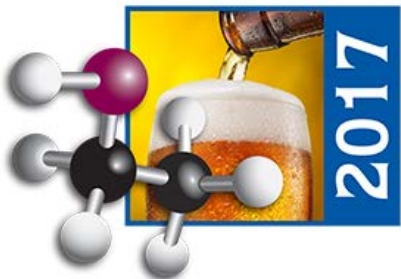
Introduction

Kim Hofecker, Manager Analytical Services

MillerCoors Brewing Company

Milwaukee

Overview of Material

- Fundamentals of Laboratory Program
  - Understanding our role
  - Goals of a lab technician
  - Basic requirements
  - Lab Best Practice
  - Delivering the Best Results
- Improving data reliability
- Monitoring Performance using key indicators

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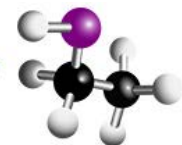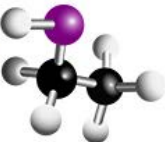
Fundamentals

- Test:
  - Describe, in <u>1 word</u>, what the main job of a person that works in any quality lab is?
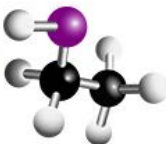
- Measure
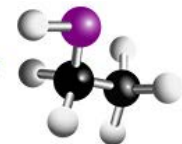
Measure

- Definition
  - verb
  - ascertain the size, amount, or degree of (something) by using an instrument or device marked in standard units or by comparing it with an object of known size

Why do we Measure?

- To ensure the preferred brand profile parameters are met
  - Most importantly it tastes, looks and smells like it should
- Brand/Product Integrity
  - To ensure products are the best they can be
  - To improve the process
- To gain efficiency
- To blend off deviations
- To meet regulatory requirements and label claims

Goals

- If we've established that our main role in the lab is to measure, then the primary goal for anyone doing the measurement / Lab Technician is:

  To provide the most accurate measurement possible

Goal – To Measure the Best!

Inputs → Pipette technique · Calibration · Training · Sampling protocol · Glassware cleaning · Reagent prep · Control programs · Good working equipment · Standard Operating Procedures · Log books → Output → Measure the Best

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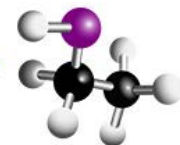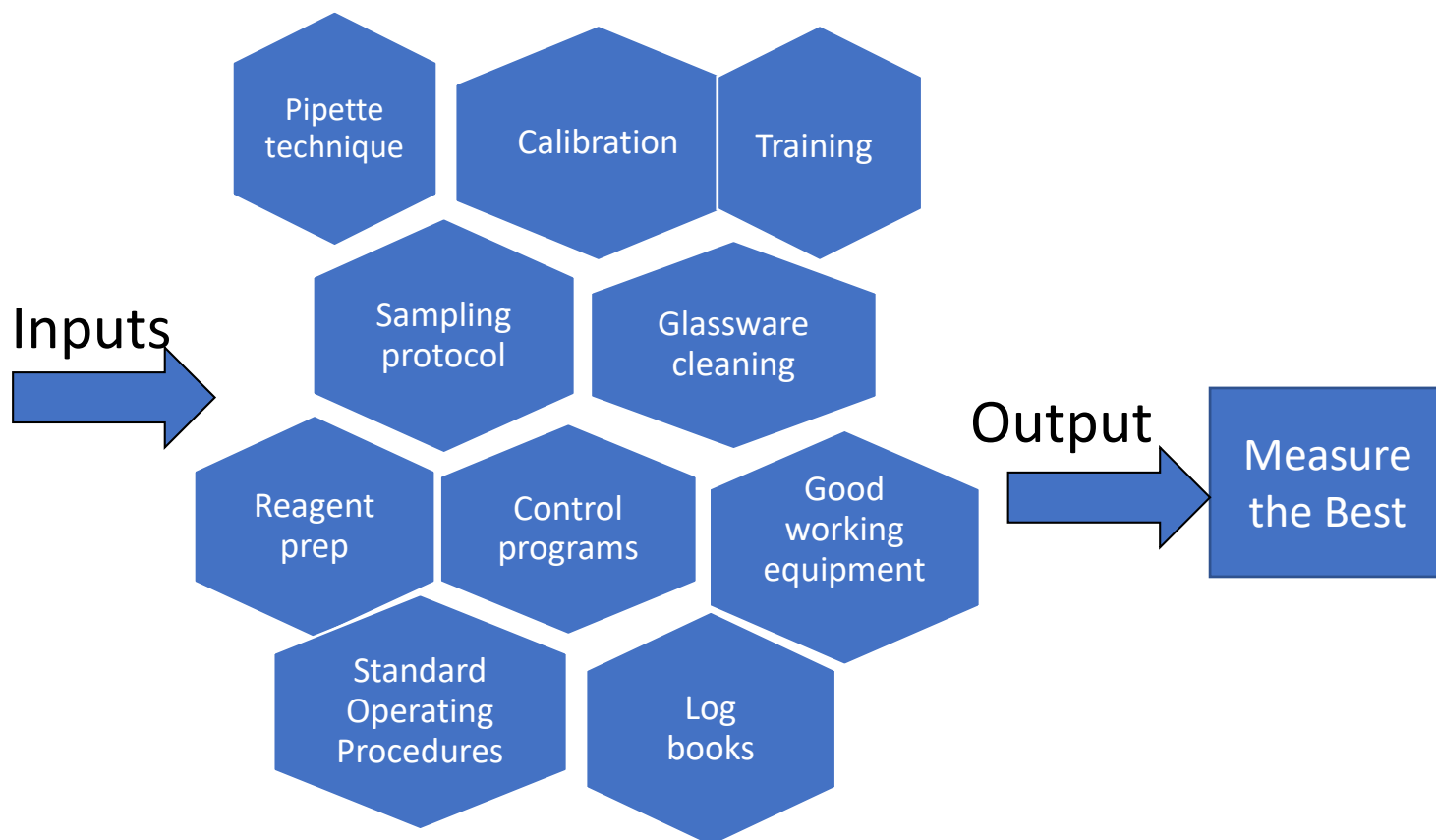
Lab Manager Responsibility

- What does it take to be able to provide the most accurate measurement?

- Map the process so that you understand potential failures

Process Map for VDK Analysis

Albany Product Lab Process: Fermentation Samples Analyzed for VDK

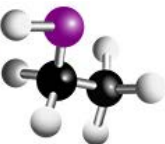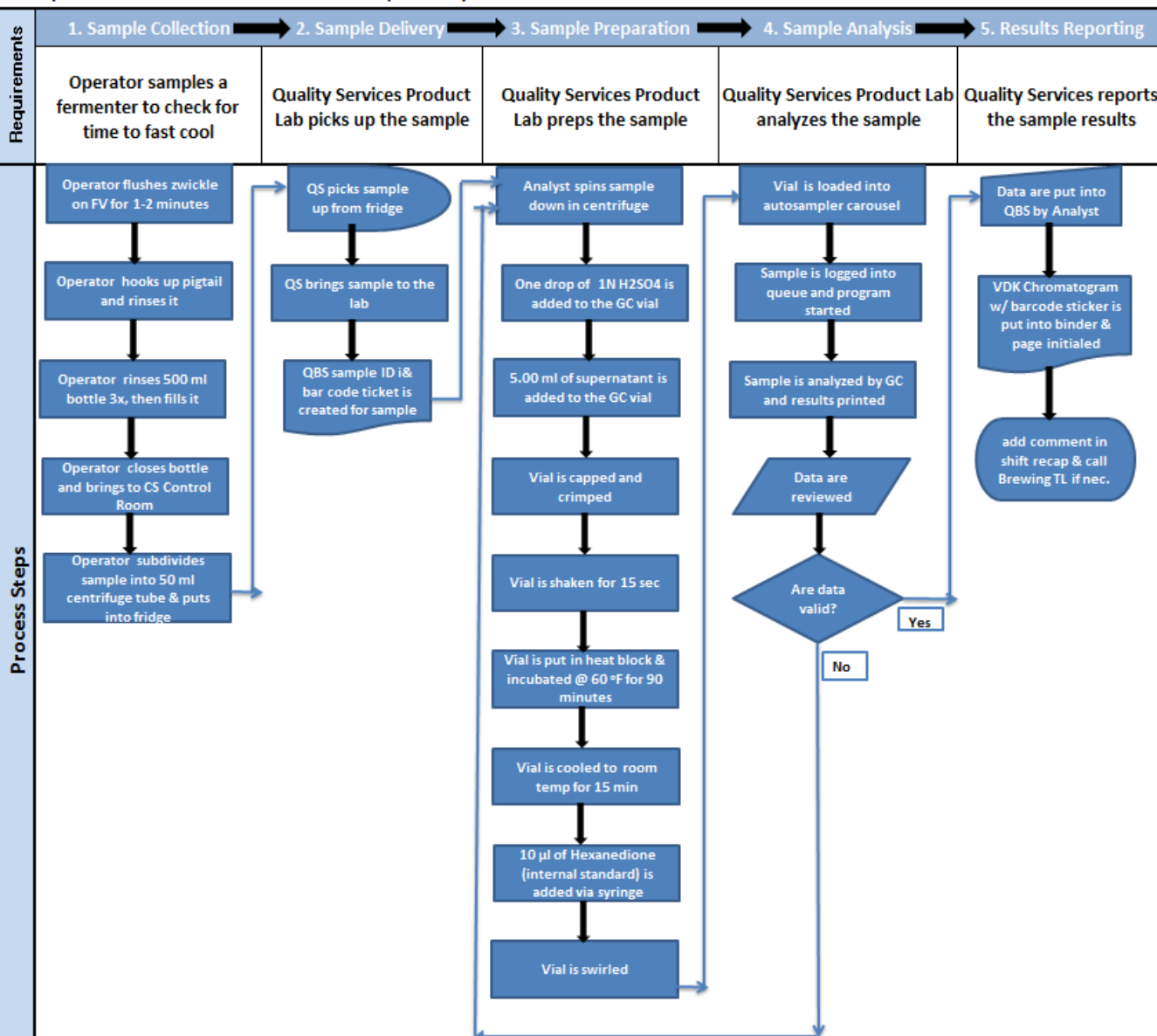| Requirements	1. Sample Collection	2. Sample Delivery	3. Sample Preparation	4. Sample Analysis	5. Results Reporting
	Operator samples a fermenter to check for time to fast cool	Quality Services Product Lab picks up the sample	Quality Services Product Lab preps the sample	Quality Services Product Lab analyzes the sample	Quality Services reports the sample results

Process Steps

- Operator flushes zwickle on FV for 1-2 minutes
- Operator hooks up pigtail and rinses it
- Operator rinses 500 ml bottle 3x, then fills it
- Operator closes bottle and brings to CS Control Room
- Operator subdivides sample into 50 ml centrifuge tube & puts into fridge

- QS picks sample up from fridge
- QS brings sample to the lab
- QBS sample ID i& bar code ticket is created for sample

- Analyst spins sample down in centrifuge
- One drop of 1N H_2SO_4 is added to the GC vial
- 5.00 ml of supernatant is added to the GC vial
- Vial is capped and crimped
- Vial is shaken for 15 sec
- Vial is put in heat block & incubated @ 60 °F for 90 minutes
- Vial is cooled to room temp for 15 min
- 10 µl of Hexanedione (internal standard) is added via syringe
- Vial is swirled

- Vial is loaded into autosampler carousel
- Sample is logged into queue and program started
- Sample is analyzed by GC and results printed
- Data are reviewed
- Are data valid? — Yes / No

- Data are put into QBS by Analyst
- VDK Chromatogram w/ barcode sticker is put into binder & page initialed
- add comment in shift recap & call Brewing TL if nec.

Main steps are across the top.

Each action associated with that step are in the column.

Shapes have meaning:
- Block = step
- Diamond = decision
- Wavy block = paperwork/document
- Trapezoid = input/output
- Bullet = delay or wait

Process is as detailed as possible. Even a little step could be the problem!

Presented by Ruth Krywicki during World Brewing Congress 2016

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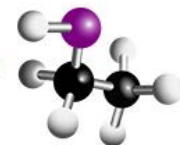
Basic Lab Requirements

- Safety –
  - Eyewash stations/ showers
  - Chemical fume hood/ microbiological hood
  - PPE – gloves, aprons, safety glasses
  - Labeling (MSDS)
- HVAC – temperature and humidity
- Dedicated electrical circuits
- Ultrapure water
- Solvent, acid and base storage
- Autoclave
- Centrifuge
- Sample prep area
- Dishwasher/ sinks – drying racks
- Volumetric glassware / pipette
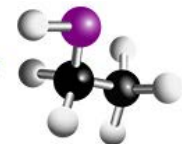
Measurement Steps - Overview

- Sampling – Collection and Delivery
  - If you don't pull the sample properly, your data is meaningless
- Sample Preparation
  - If you don't prep the sample properly, your data is inaccurate
- Sample Analysis
- Results Reporting
- Data Trend / Reaction
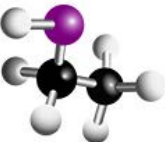
Sampling Protocol

- Have and Follow Standard Operating Procedure (SOP) when sampling – uniform time - drives consistency

- Minimize foaming (especially important with BU and hop analysis)

- Use clean sampling coils and containers

- Allow enough time to rinse the sampling line in order to get a fresh and representative sample

- Rinse the sampling container with the product prior to filling it

- Do not allow samples to sit on the bench for extended periods prior to analysis

- Unless you are analyzing immediately, store samples cold and in proper containers – freeze?

- Sample consistently (time during process that sample was taken)

- If you get unexpected results, re-sample
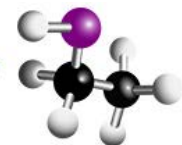
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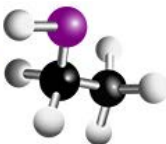
Sampling
Sample Flask Cleaning Procedure

- Use a dishwasher, if available with a mild soap such a Tergazyme or Alconox in cycle

- Alternative – Make a tub of soapy water to soak in

- Designate glassware/flasks for particular uses to prevent contamination

- Rinse with solution that you are sampling

- Discard old Nalgene sample containers as needed

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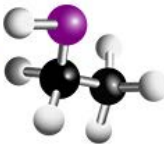
Sample Preparation

- Have and follow a Standard Operating Procedure
- Dilute volumetrically, if necessary
- Follow consistent de-carbonation procedure
- Filtering/centrifuging
- Thawing procedures
- Attemperation
- Correct sample size as well as volumetric flasks
- Special considerations i.e. volatiles, freshness

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Standard Operating Procedures "SOP"

- This is our Playbook

- Located in a place easy to access

- Standard format

- Use as a reference for safety, analysis, sample prep procedures, reagent preparation procedures, reagent shelf life, storage condition, approved consumables etc.

- Annual review process for updates

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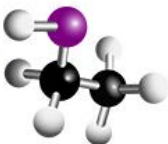
Training Program

- Formal lab program with re-certification
  - Safety, instrument operation, theory, reagent preparation, calibration, maintenance, troubleshooting
- Proven proficiency – can use Validation Program / collaborative samples for this

  Don't train folks to just push buttons

Equipment Working Well

- Good Calibration – set acceptable limit for R^2 (value ≥ 0.995 is ideal), track changes from last calibration and have a standard to ensure slope is in correct position

- Maintenance/PM program

- Record keeping / Log book

- Consumables on hand – routine and break/fix

- Track Key Indicators of Performance – pressures, baseline, absorbance units

- Utilities / Surge Protection

Calibration and Maintenance Records

- Maintain a log book for each individual instrument

- Record routine maintenance as well as break/fix issues

- Record Manufacturer's PM's and include the condition and recommendations from technician

- Track key indicators of good calibrations i.e. r^2 value, slope, change in calibration amounts, pressure

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Reagents/ Reagent Prep

- Store reagents per manufacturer's recommendation (temperature requirements)
- Do not use expired reagents
- Refer to SOP's for stock and working standard reagent shelf life
- Prepare and store according to instructions in SOP
- Refer to Certificate of Analysis for purity information
- Designate glassware for particular uses to prevent contamination
- Practice good pipette technique
- Rinse with solution that you are preparing – If preparing VDK calibration standard in 5% ethanol, rinse volumetric flask with 5% ethanol prior to

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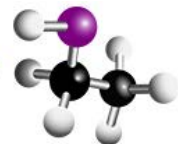
Product Specifications

- They enable us to make consistent products
- Easy access with clear reactions to deviations

Your lab techs must know what is acceptable variation and how to react when it's not!

Monitoring Performance Using Indicators

- Data analysis and Trend Reporting

    - How do I know that I'm producing accurate data?
   - How do I prove that I'm producing accurate data?

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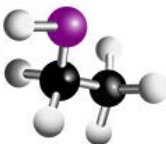
Developing a Robust Control Program

- Ideally a control program should consist of the following:
  - A standard that is certified to contain a known quantity of the compound that you are analyzing (Purchased through ERA, High Purity Standards etc)
  - A check beer (control beer) which has values assigned based upon statistically sound procedures
  - Verification of an unknown sample by an outside and un-biased source – Validation Program (LGC's BAPs program or ASBC Check Sample)

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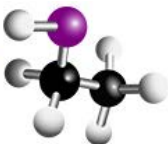
Certified Standard

- Can be purchased from companies such as ERA or High Purity Standards.

- Provides a known value to ensure calibration curve slope accuracy and to help troubleshoot

- Available standards:
  - Metals, Total VDK, 2,3 butanedione, 2,3 pentandione, Carbohydrates, DMS, iso-alpha acids, tetra hydro-hop, conductivity, pH etc.

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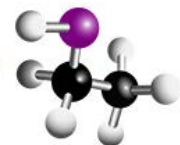
Check Beer Program

- How to establish assigned values:
  - Collect a large quantity of beer from the same batch and store it cold
  - Randomly select a can/bottle from each layer of the pallet(s) and analyze for all analyses performed within the lab
  - N=25 or more
  - Do not run all the analysis on one day/shift/ analyst. Spread this out.
  - Obtain average and standard deviation
  - Create your LSL and USL by doubling your standard deviation (2 sd's - 95% confidence level)
  - Create control charts based upon this
  - If you have multiple labs, use same Check beer for all

  Note: Your system must be stable and in good working condition. Use a certified standard or BAPS sample to ensure accuracy.

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Robust Control Program – Things to consider

- Post acceptable values near instrumentation so that everyone is aware
  - Utilize the control for as many analyses as possible
  - Post acceptable ranges such as Alc v/v 3.22 – 3.25
  - React to these ranges. Do not report data if your controls are not within the limits
- Chart the values on a running control chart that is kept near the instrument
- A control sample should bracket your results…beginning, after 10 and at the end
  - Do not utilize one control sample for a large run. If it's out of range, then the data can't be assumed to be accurate
- Controls should be of similar nature to that which you are analyzing
  - May need to have multiple check beers to cover the range of product to be analyzed

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Monitoring Performance Using Indicators

| Define Process/ Program to be Monitored | Identify Performance Metrics | Develop Performance Metrics | Monitor Metrics | Perform Data Analysis | React to Data Analysis | Determine Improvement Activities |

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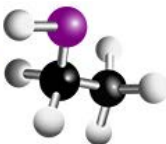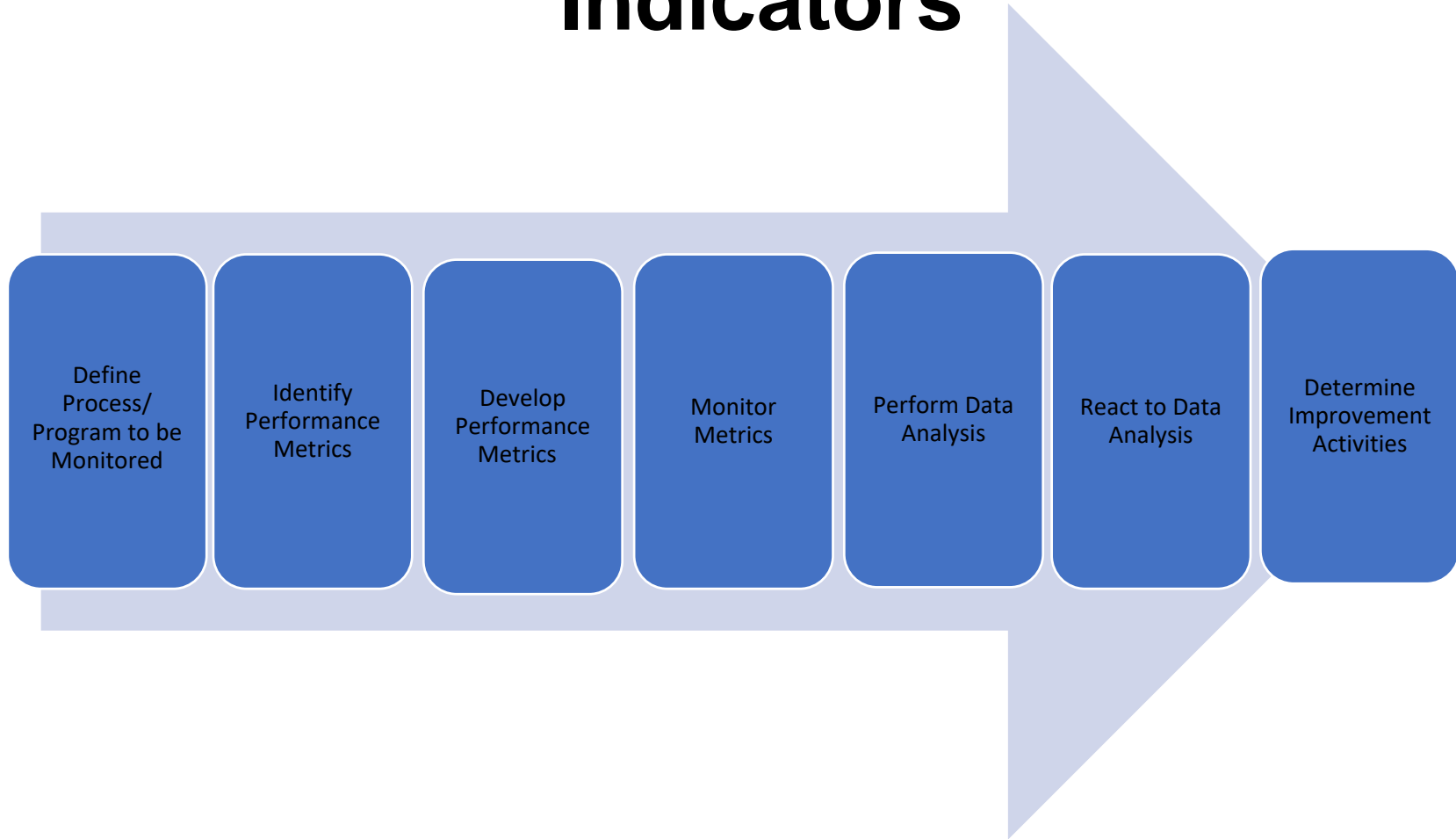
Monitoring Performance Using Indicators

1. Define the process to be monitored
   - For laboratory purposes, this could be any analyses
2. Identify process metrics
   - Value of a control beer, assigned value of a BAPs sample or certified standard (ERA), area counts of calibration standards (% change)
3. Develop process metrics
   - N=25 and develop average, LSL, USL (+/- 2 sd's)
4. Monitor metrics
   - Routine analysis of control at beginning, after 10 and end of run
5. Perform data analysis
   - Trend data using a control chart
6. React to data analysis
   - Standard statistical rules dealing with outliers and trends
7. Determine improvement activities
   - Re-calibrate, perform maintenance activities
     - Be careful though to not tweak too much!

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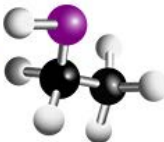
Control Chart
Introduction to Normal Distributions

- The Normal Distribution follows a bell shaped curve and is a versatile model used in SPC
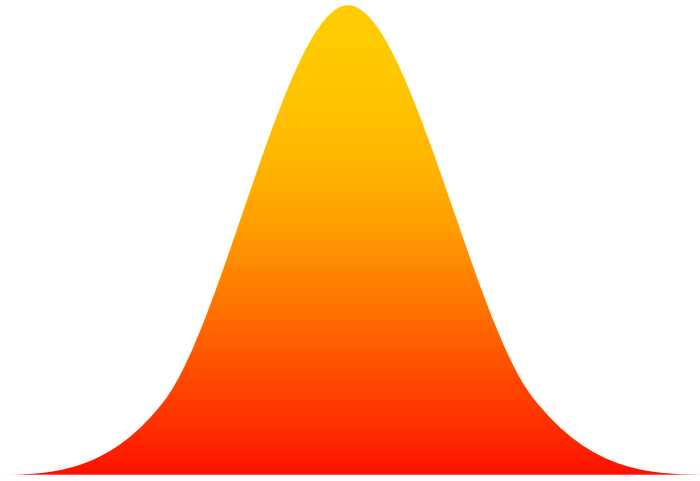
- Two Parameters that define the Bell Shaped Curve:

   1) Average, Mean, or Center of the distribution (Assigned Value)

   2) Standard Deviation or Spread of the distribution

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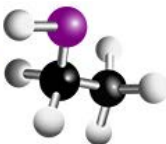
Control Chart
Introduction to Normal Distributions

Population Mean or μ

- The population mean μ falls right in the middle of the bell curve

- 50% of the bell curve falls on either side of the mean

- Mean represents an expected value

μ

- We never know the true mean, μ. We can estimate it from a sample of data by calculating the average of a sample
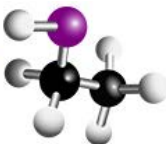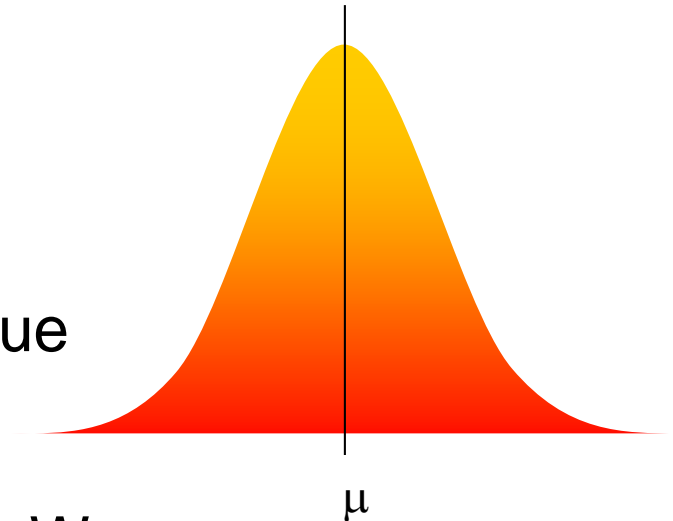
Control Chart
Normal Distributions

Standard Deviation, σ
Standard deviation measures the spread in the data

Key Point: Virtually all of the data from a normal distribution falls within +/- 3 standard deviations from the mean

99.7%

95.5%

68.3%

1σ   1σ

μ

2σ   2σ

3σ   3σ

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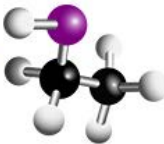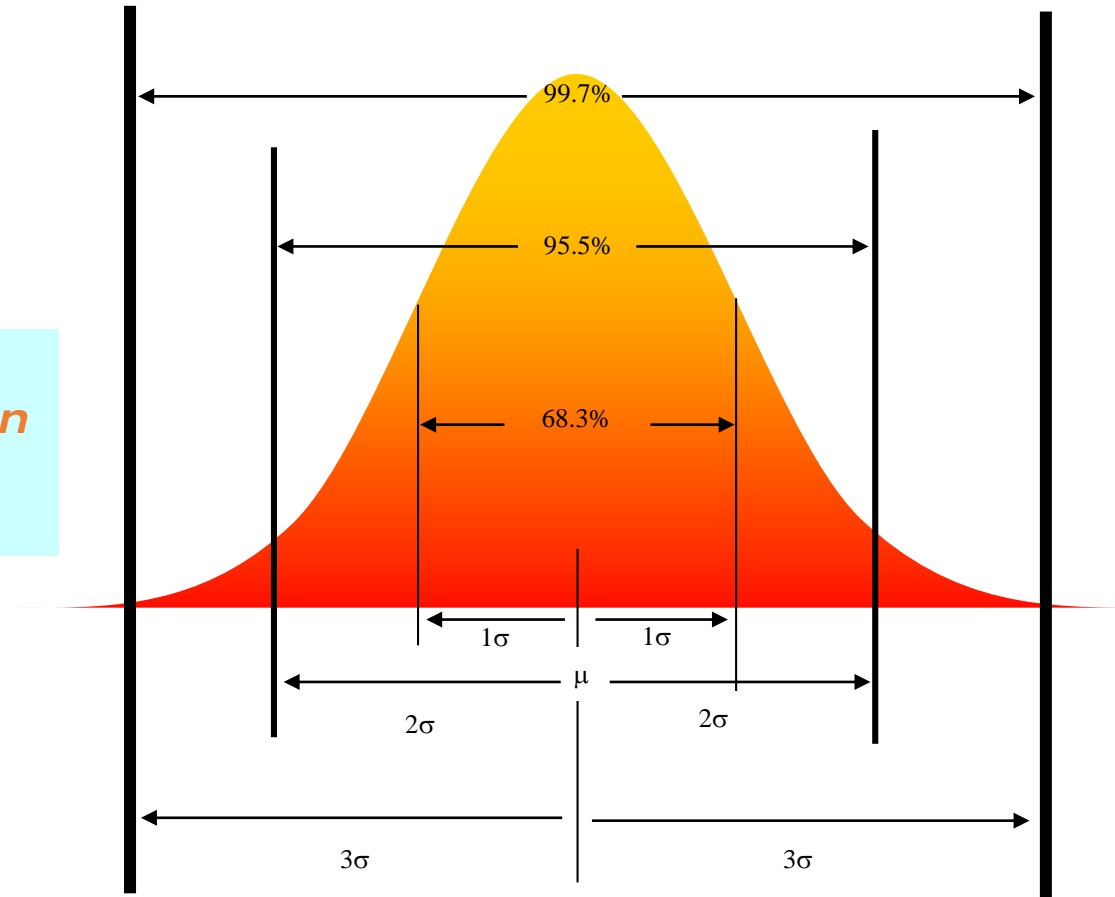
The Control Chart

• So how do we monitor our processes?

If we collect data on the process, we should have some idea on where the average is and the spread

From this, we should be able to create a chart with control limits where we think we will see results
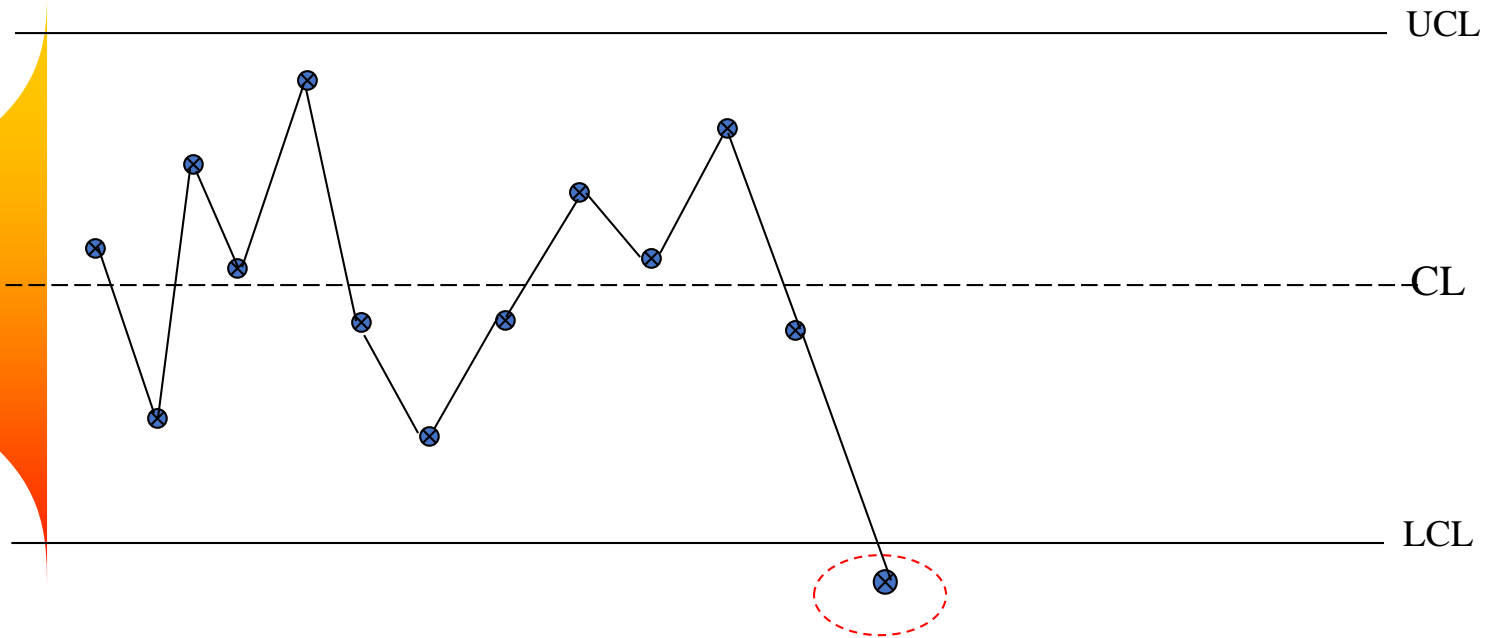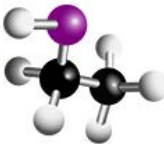
UCL

μ

LCL

μ

The Control Chart

UCL

CL

LCL
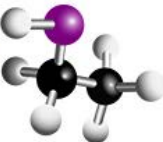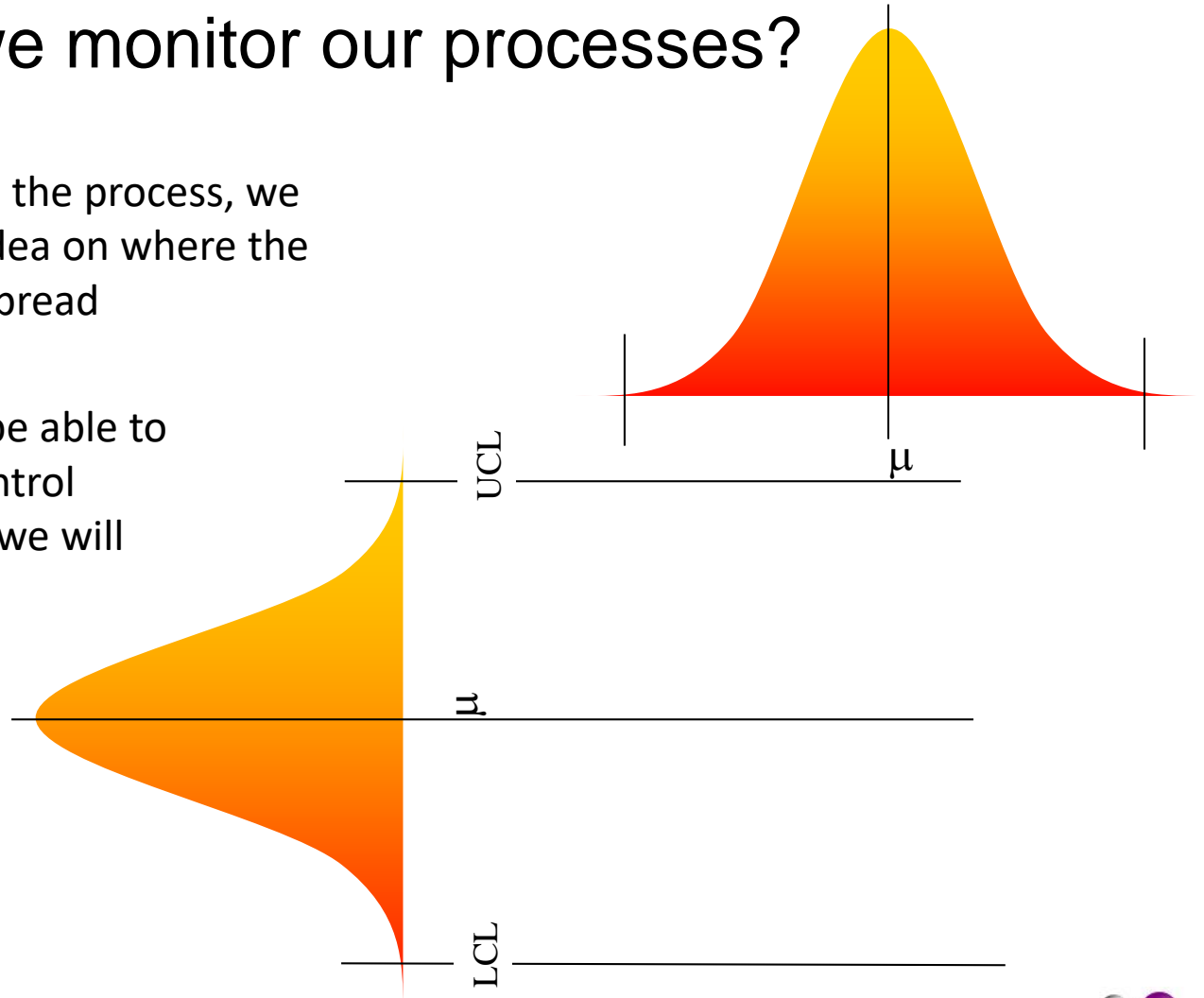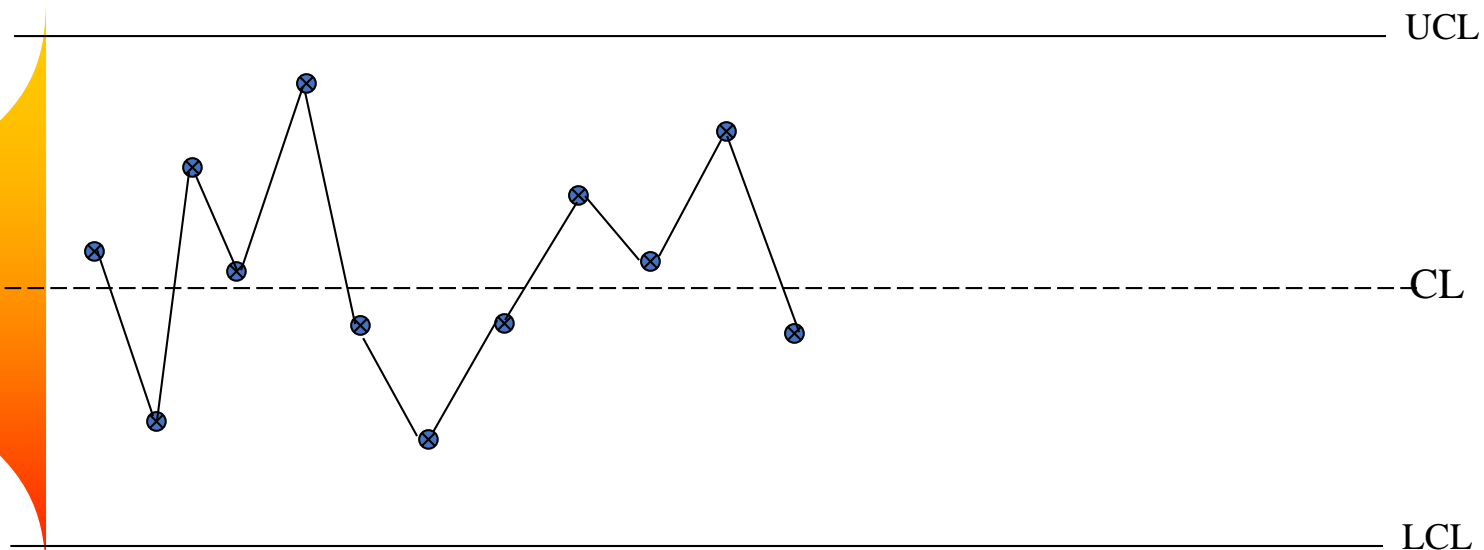
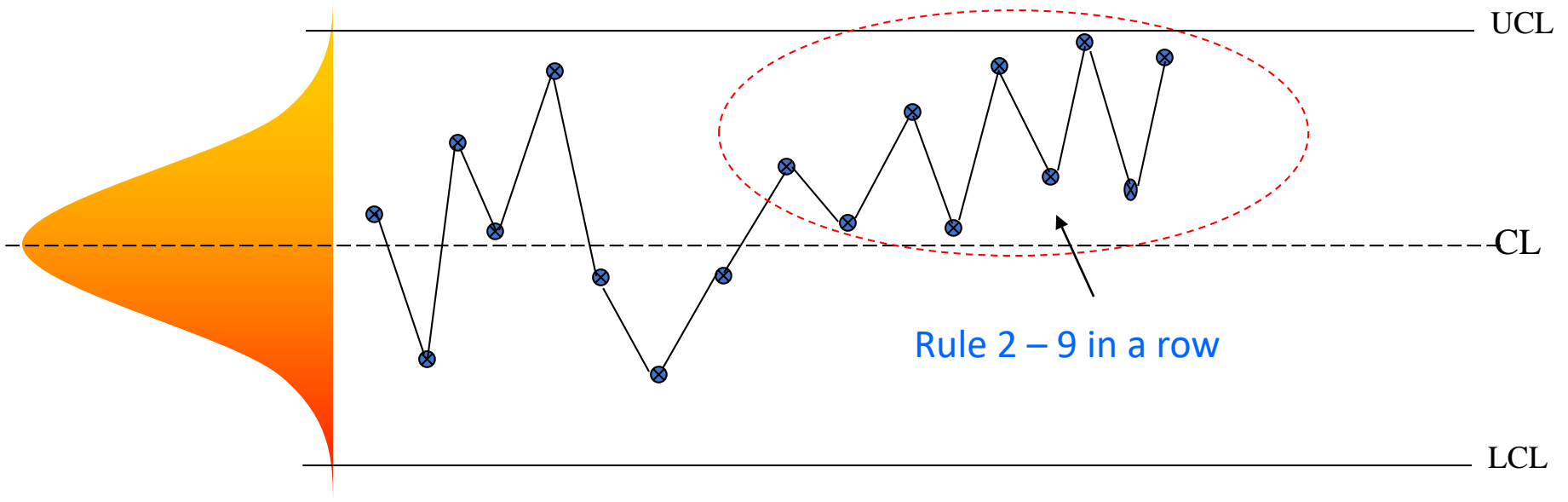As we get a new data point, we put that on the control chart and note where it falls
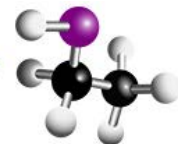
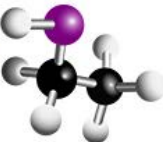# Rule 1: Anything outside of Control Limits

Since it has fallen outside of the control limits we must assume assignable cause variation is present
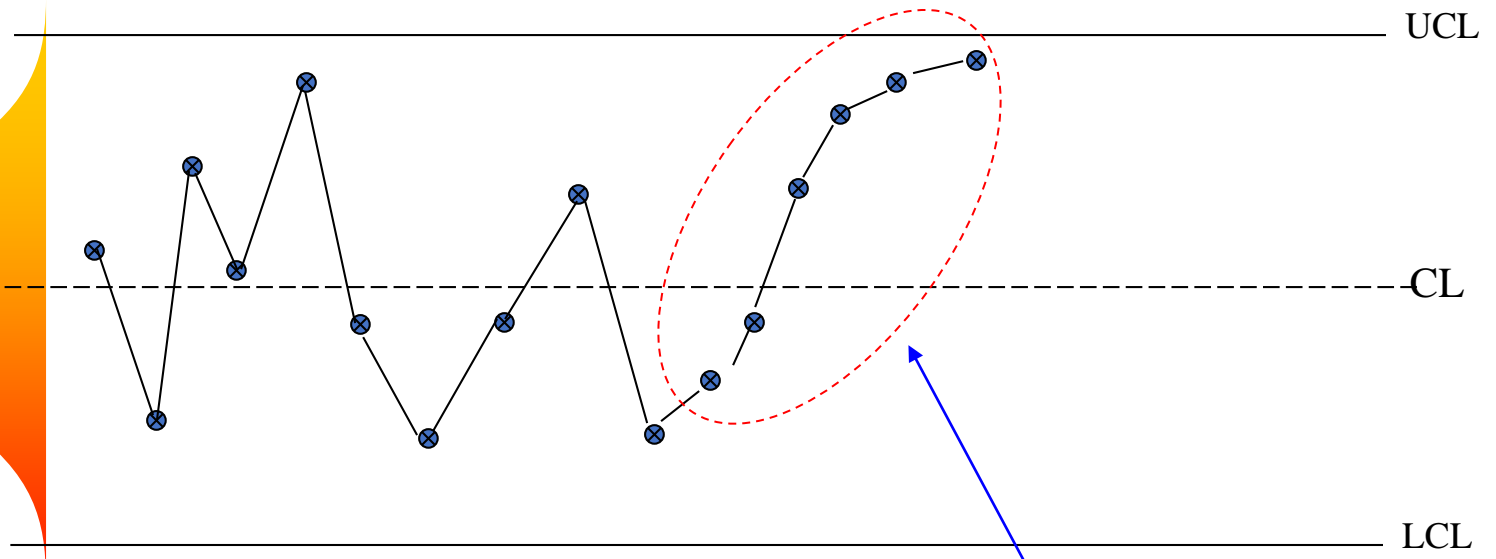
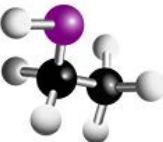# Rule 2: Run of 9 on one side

Rule 2 – 9 in a row

UCL

CL

LCL

Rule 3: 6 Points Trending

UCL

CL

LCL

Rule #3 – 6 consecutive increasing/decreasing

Summary

- Getting good data from a lab isn't as easy and straightforward as it seems

- Ensure basic requirements are met

- Treat each analysis as a individual process / map it so you understand potential failures

- Train the personnel to understand the holistic process

- The most robust results can be obtained when you monitor your lab performance using Key Process Indicators

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